Theoretical Considerations and Clinical Study

MAMELDIN

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Research, Production, Pharmaceuticals

Theoretica Considerations

Mameldin cream is a modern therapy based on plant extracts having at their base interactions between the chemical and physiological actions which correspond to cellular receptors in the mammary tissue and other hormonal-dependent tissues, thus affecting the prolactin actions. Through this action, it prevents certain secondary disorders such as dysmenorrhea, pre-menstrual syndrome, breast pains, prolactinic dysfunctional hemorrhages.

The menstrual cycle is determined by the interactions of hormones integrated in the hypothalamus-hypo-physio-ovarian system, and, a normal menstrual cycle assumes the correct function of a series of organs (nervous system, endocrine system, Hematopoietic system, etc.), as well as a perfect interrelation between the hormones secreted b the two systems (especially the concentration and the feedback of the secretion of these hormones). Even very small fluctuations in serum of a single hormone can lead to disorders in the menstrual cycle and can lead to a series of pathological states from simple to complicated, and to potential severe health complications.

One of these hormones, whose importance in the menstrual cycle of women, demonstrated in the last few years is prolactin, It was improperly named a luteotrophic hormone, due to the fact that it stimulated the development and secretion of a yellow body (corpus luteum) in certain species, such as in rodents.

From a phylogenetic standpoint, prolactin is one of the oldest hormones, having been detected in fishes, reptiles and mammals. If in mammals it is essential in the lactation process, in reptiles and in fish as well as in birds it is implied in other functions connected to reproduction.

It was isolated as an independent molecule in 1972 by Hwang. In the years following, it was studied in human physiology and in its pathological implications.

Prolactin is a hormone associated primarily with lactation; during the breast-feeding, the child stimulates the mammary receptors whose excitement reach the central system (hypothalamus – hypophysial) and as such stimulates the production of prolactin which fills the mammaries with milk by the process of lactogenesis, readying it for the next feeding. In much the same manner, oxytocin also acts the same way by contracting lactiferous duct and ejecting the milk.

The production and regulation of prolactin secretion

Prolactin is synthesized by lactotroph cells by the interior pituitary as much in the male as in the female; it is also produced by other tissues, such as the decidua. At the hypophysial level, the concentration of prolactin is around 200 μg, and the plasmatic half-life is around 30 – 40 minutes; even so its presence persists a very long time due to the hormone binding to lactogenetic receptors. At the receptor level, prolactin can be detected even at 2 days.

As a structure, prolactin is a polypeptide formed by 196 amino-acids with a molecular weight of 23,000 Daltons. Its structure is similar to the somatotrophin hormone with which it was for a long time assimilated, the somatotrophin also possessing lactogenetic properties.

Prolactin secretion is regulated at the hypothalamus level by neurosecretory neurons, the most important being dopaminergic in the nucleus which secretes PIF (Prolactin inhibiting factor); this gets to the hypothalamus-hypophysial port by the Gr. T. Popa & Fielding at the interior hypophysial level and inhibits the prolactin secretion.

TRF (Thyreotropin Releasing Factor) stimulates the release of prolactin by inhibiting the PIF. These aspects are discussed in detail below. Hypophysia as secretion spot of prolactin is subject to neurosecretory factors.

If the removal of the hypophysial is successful, prolactin secretion and as a result lactation are interrupted; contrary to hypophysectomy which interrupts lactation, the sectioning of the pituitary rod which connects the hypophysial to the hypothalamus, raises prolactin secretion while the secretion of other hormones drops dramatically.

Based on this, presumptions have been made as to the hypothalamus' role as an inhibitor in the release of prolactin; hypothalamic extractions have been found to have an inhibiting role as much in vitro as in vivo over the release of prolactin.

The hypothalamus secrets PIF (Prolactin inhibiting factors) assimilated with dopamine which inhibits prolactin release.

Dopamine, known as an adrenergic neurotransmitter also has the distinction of local hormone. Released by the arched nuclei of the hypothalamus, its primary function is the inhibiting of prolactin release from the inner lobe of the pituitary. As such, besides the other central avenues of dopamine (mesocortical, mesolimbic, nigra-striata), the dopaminergic pathway represents and important link between the pituitary and hypothalamus.

Substances which block dopamine receptors (anti-psychotics) determine the growth of prolactine and lactation disorders, menstrual cycle, headaches and sexual dysfunctions. These effects suggest dopamine's implication in the regulation of pregnancy mood, maternal behavior and sensory sensitivities in general.

Another important modulating function is the one held by dopamine at the basal nodes in the control of motility. The decrease in dopamine from the nigra-striata determines the appearance of Parkinson's disease, affecting muscular control and voluntary movement.

In the frontal lobe, dopamine controls the flow of information which arrives from other zones. Alterations to the dopamine level in these regions causes the decline in neuro-vegetative functions especially the memory, attention and problem resolution capacity. Another area where dopamine plays a role is the motivation of positive and negative factors of stimulating pleasure and fun activities. These factors are important for the behavior relating to food and sex, with negative consequences with the use of drugs such as cocaine and amphetamines, which inhibit dopamine recapture, increasing the time the drugs affect the brain.

If PIF secretion falls prolactin is released; if PIF secretion is increased, prolactin secretion falls or is stopped.

In contrast to the release of the other pituitary hormones, the release of prolactin from the pituitary is done through inhibitors, therefore inhibiting inhibition means excitement, therefore prolactin secretion. In other words, the hypothalamus acts like a blocking system over the release of prolactin; if the block is removed, release of prolactin occurs.

Numerous neuro-transmitters inhibit or stimulate the release of prolactin; however, in this context dopamine plays the most important role; the release of dopamine-energetic neurons, directly in the hypothalamus-pituitary system where it inhibits the release of prolactin.

GABA, beta-endorphins, VIP and angiotensin II have inhibiting actions over the release of PIF; these substances, inhibiting PIF, determine the secretion of prolactin. By the same mechanisms, there is an increase in prolactin secretion following stress (traumas, surgical procedures which increase the release of opioid substances from the melanocortin group), after the administration of contraceptives based on estrogen (which raise prolactin by raising the number of lactotropic cells), afther the administration of psychotropic drugs, TRH, dopamine antagonists, serotonin or serotonin agonists.

Pain of any kind, somatic, visceral or mental determine the secretion of protective substances (for pain blocking) at the central nervous system level which registers pain, namely the melanocortin which by enzymatic reactions gives birth to ACTH, melanin, endorphin; these manifest inhibitory actions over PIF and dopamine, and the inhibition of PIF determines the increase of prolactin secretion. This explains amenorrhea and menstrual disturbances in mental traumas.

Serotonin or 5-Hydroxytryptophan functions as neuro-transmitter substence as well as local hormone; it actions as inhibitor against cerebral functions (dopamine) and cerebro-spinal nociceptive; the seratonin-catecholamine cerebral balance ensures the maintaining of sanguine pressure, boy temperature, food ingestion (digestion) as well as psycho-active in normal limits.

The administration of L-dopa, precursor to dopamine leads to the increase of dopamine quantity, therefore PIF, which has a secondary effect the suppression of prolactin secretion; for this reason L-dopa can be used to reduce prolactin secretions and amenorrhea-galactorrhea syndroms which as a result follows the decrease in galactorrhea and menstrual syndrom effects.

Furthermore, administering 2-alpha-bromocriptine, semi-synthetically created with ergotoxine alkaloids (found in rye) reduces prolactin secretion by increasing the tonus of dopamine neurons. What is interesting are the relations between TRH and prolactin. Administering TRH leads to the increase of TSH secretion and secondary prolactin secretion. In clinical or subclinical hypo-thyroidism, TRH secretion is increased by feedback mechanism which leads to PIF inhibitor in hypothalamus, a fact which increases prolactin secretion. Theincrease in prolactin secretion leads to disturbances in menstruation as well as amenorrhea by compensatory reduction of the other pituitary gonadotrophes.

The normal concentration of prolactin varies with each woman after each cycle, generally within 5 – 20 ng/ml. The largest serum concentrations are in the luteal phase of the menstrual cycle; as well, smaller concentrations are before menarche only during reproductive phase.

This fact determines some authors to consider that estrogen has a stimulating role on the secretion of prolactin. In this sense, a close link between sexual hormones and lactotrophic cells in the anterior pituitary; after administering estrogen the number of these cells grows, as well as prolactin secretion. During pregnancy, the pituitary gland's volume almost doubles and the concentration of prolactin grows progressively, probably due to the dopamine-antagonistic actions of estrogen (lowers PIF secretion).

Hyper-prolactinia is determined by:

1. Stress levels (different pains, surgical procedures, traumas, conflicts and negative emotions) which determine the secretion of opioid substances at the encephalon level as a protective measure. Opioid substances in their own way have inhibitor effects against dopamine and in this way stimulate hyper-secretion of prolactin (dopamine inhibits prolactin secretion; if dopamine is inhibited, or lowered, prolactin secretion grows).
2. Medication (etiologic iatrogenic) with sedative and hypnotic actions, tranquilizers, neuroleptics, anti-depressants, opioids or anti-conceptionals. Taking into account that hyper-prolactinia modifies the link between pituitary gonadotrophes in the sense that it does not influence FSH secretion but lowers LH secretion, it is understood that through this mechanism, hyper-prolactinia becomes secondary cause to the insufficient maturation of the ovarian follicle or the non-corresponding functions of it (which can become ovarian cysts or insufficient yellow body). This fact brings us to the modification of the estrogen-progesterone balance in favor of the estrogen, which are implied in a series of morbid syndromes: pre-menstrual syndrome, mastodynia, cystic mastopathy, dismenorrhea, hemorrhages, infertility, etc.

Action mechanism of Mameldin Cream

Mameldin contains as principal active substances a complex of plant extracts from Vitex agnus castus (Chasteberry), Heracleum sphondylium (Common Hogweed). In vitro studies have shown that Vitex agnus castus and Heracleum sphondylium extracts inhibit the secretion of prolactin at the pituitary level.

In vivo studies on rat populations that have been stressed have show important increases in prolactin secretion; after the administration of Vitex agnus castus and Heracleum sphondylium the prolactin rise during stress was insignificant. This fact is explained by the dopamine agonist mechanism of the principal active ingredients in both Vitex and Heracleum.

The administration of extracts from both plants on female rats during lactation phases determined the inhibiting of lactation preceded by prolaction inhibition.

Other studies have demonstrated that the properties of the Vitex agnus castus compontents for inhibiting beta-estrogen receptors from the heart, bone, urinary tract and in blood vessels.

In women with hyper-prolactinia, the extracts inhibit the release of prolactin and normalize the deficiencies in the luteal phase.

The primary active ingredients in Vitex agnus castus & Heracleum sphondylium inhibit the growth of cancer cells at the breast level, the ovary and the cervix, stomach and colon. Cyto-toxicity is linked to the rate of cellular growth, cellular death being attributed to intercellular oxidation. Cyto-toxicity from the extracts of Videx & Heracleum over the cancerous cells is attributed to the composition of flavonoids and polyphenols which amongst other properties, induce apoptosis in cancerous cells.

Statistical studies of over 50 years have demonstrated therapeutic effects of maximum importance of the Vitex & Heracleum extracts in improving menstruation and the effects of certain hormonal imbalances, such as PMS, mastodynia, mastopathy, etc).

Pre-Menstrual Syndrom

PMS is represented by a complex of mental symptoms, vegetative and emotional whch appear in the luteal phase of the menstrual cycle and is finished in the follicular phase.

Approximately 40% of women suffer from PMS and around 10% of these show severe cases which impede them from normal activities.

Mastodynia is considered as being the principal manifestation of PMS, however it can also appear independently. It is characterized by pains in the mammaries which appear before menstruation, feelings of tension at the breast level or heaviness (pressure). Mastodynia can be permanent with PMS or in the days leading to menstruation. Pain can be spread to the breast periphery or along the arms.

Mastodynia as painful symptom of the breasts, can be linked with migraines, exhaustion, localized pain, bloating, cramps, diarrhea, constipation, increase in breast volume, articulation and muscle pains, dizziness, lowering of the libido, acne aggravation, or some fungal infection.

Even though PMS is not completely understood, a hormonal imbalance and an increase in prolactin levels have been observed. As it follows, any treatment with prolactin lowering factors has been proposed.

Mastopathy is a benign modification at the breast level and is one of the most frequent breast diseases in women. It appears in 20% of women and is present in pre-menopause. After menopause, no new cysts appear. This fact shows the role of ovarian steroidal hormones in the etiology of this disease.

In conclusion, mastopathy and mastodynia directly affect the estrogen-progesterone balance represented by an increase in estrogen and decrease in progesterone secretion and interfere with prolactin at the mammary receptor level.

Mameldin cream contains a mix of extracts of Vitex agnus castus and Heracleum sphondylium which act locally, at the mammary receptors where they bloc prolactin actions.

Clinical Case Study

The cases have been taken by Dr. Viorical Leica,

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Case 1

S.E., a 50 yr old female, taken in on 18.5.2006, for bilateral cystic mastitis, and right breast galactorrhea. It has been determined that patient's mother also died on 2005 with a neoplasm in the same breast.

FCB is recommended with cultures from breast sample, radiography, and prolactin dosing. The laboratory results show: golden staphylococcus, sensitive to norfloxacin, gentamicin, and chloramphenicol; radiography in normal limits; prolactin 5.3 μg (normal 2.39 – 2.51 μg). Treatment with Utrogestan pills XX, 2 / day from 15th day, for 10 days and Progestogel intermittently for 6 months; galactorrhea persists. From september 2006 bromcriptin is administered, 20 pills, 2 / day until January; galactorrhea persists. In January of 2007, vaccine performed for staphylococcus. Bromcriptin treatment continues, 2 pills / day for 2 months, together with Heracleum Sphondylium (Common Hogweed) tea for a few months. Galactorrhea persists. Once more prolactin is dosed. It is now double (5.6 μg). In June 2007 tumor markers for the breast, uterus and ovaries are ordered (results are within normal). Radiography is repeated as well as microbial culture from breast secretion. Results are normal. After a 9 month period, patient returns in June 2008 with the same symptoms. Ultrasound and mammogram are repeated. In the ultrasound exam, cystic mastitis is found, without calcification and lymphadenopathy, images confirmed by the mammogram.

In September 2008 Mameldin cream treatment is applied. After 3 tubes of Mameldin, galactorrhea diminishes significantly. The Mameldin treatment continues, the tumor markers are repeated, prolactin and bacterial culture in December 2008. In the culture, non-hemolytic streptococcus appears. Antibiotic treatment follows; prolactin is triple: 9.5 μg. During this time, patient undergoes domestic problems (divorce). Continues treatment with Mameldin. After 3 years from initial diagnosis with galactorrhea, in January 2009, after Mameldin treatment, a good evolution is shown with the absence of galactorrhea; the same results are maintained in February and to this day.

Case 2

P.M, 59 yr old female, pharmacist, with mastitis in the left breast seen in July 2006, has ultrasound exam; the diagnosis of cystic mastitis is confirmed. Treatment with Progestogel follows as well as Mastodynon, for 4 – 5 months (July – November 2006). During a follow-up examination, small improvement. In Mai 2007, left breast shows signs of lymphangitis, mammary retraction, cystic mastitis for which

treatment with Progestogel, Diclofenac was ordered. During this time, different treatments are administered. Most conditions improve partially. In March 2008, patient came back for examination. Again, the diagnosis of cystic mastitis is confirmed. Stressful life events occur for patient (divorce). Same treatments as above continue. In September 2008, during clinical and paraclinical examination, the same situation is diagnosed. This time, patient is advised to take Mameldin treatment – 4 tubes and, in November, mastitis completely disappears as well as symptoms of engorgement and tension. On the ultrasound, the cystic condition shows an almost complete heal. Mammogram is normal. Mammary retraction disappears. In February (2009) all symptoms are gone.

Case 3

R.V., 45 years old, bilateral micro-cystic mastitis, examined on 23.10.2008. Patient complains of pains, tension and engorgement. Ultrasound finds the following: Right breast –moderate adiposity, micro-cystic mastitis (3.5/1.8 mm, 3.1/1.6mm, 3.5/2.4 mm), without adenopathy or calcification. Left breast: micro-cystic mastitis (3.7/1.2 mm, 2.7/2 mm) without adenopathy or calcification. Mammogram confirms ultrasound. Treatment with Mameldin follows. On 6.11.2009 clinical exam reveals total disappearance of symptoms (pain, tension), ultrasound confirms net improvement of local situation.

Product Introduction

Ingredients: Heracleum Sphondylium (Common Hogweed) and Vitex Agnus-Castus (Chasteberry), Aqua, Isopropyl myristate, Glycerin, Cetearyl alcohol, Potassium cetyl phosphate, Lanolin, Helianthi oleum, Ceteareth-20, Methylparaben, Imidazolidinyl urea, PEG-3-sorbitan oleate, Silica.

Indications: Mameldin's main function is to alleviate pain relating to various symptoms relating to PMS, specifically those relating to mastitis as well as those relating to pelvic pains, and menstrual hemorrhages.

Usage: Recommended dose is 2.5 – 3 ml cream which is applied to the surface of the breast and massaged until absorbed by the skin. 3 – 4 applications daily, including during the pre-menstrual cycle. The treatment duration can be 3 – 4 months or more, according to the rate of healing of the symptoms.

Package: 50 g tube

Shelf life: 36 months

The product has been accredited by the Ministry of Health with Notification No 47998/13.05.2008